Obstacles to Translation Conference

Summarized by Ervin H.Epstein Jr.[1], Barbara A. Gilchrest[2] and Leonard M. Milstone[3]

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STATEMENT OF THE PROBLEM

So many genes, so few therapies. This meeting* arose from the perception of the organizers that there are many discrete and hopefully correctable causes for the failure of discoveries in academic laboratories to result in new therapies. The immediate concern was for genodermatoses, individually rare disorders that in the aggregate are responsible for very substantial morbidity and mortality. Despite the identification of responsible gene mutations and often detailed understanding of the pathophysiology, effective therapies are still largely unavailable.

STRUCTURE OF THE MEETING

The two-day meeting consisted of eight sessions focused on discrete topics relevant to the development of molecularly targeted therapeutics for heritable skin diseases, followed by four breakout discussion groups and a final joint session for review of the group reports and consensus building with regard to next steps. The 30 speakers, representing critical nodal points in the drug development process, were invited to submit reading lists in advance. These lists and "slides" from most of the presentations are available at the conference web site (http://www.obstacles.medschool.ucsf.edu). Speakers identified problems that they had encountered in their work or that they perceived to be issues for development of therapies for rare skin diseases. Group discussion during each session was facilitated by a moderator, also expert in the topic area.

The meeting had its genesis in a discussion among members of the medical and scientific advisory board of the Foundation for Ichthyosis and Related Skin Types (FIRST) concerning how to stimulate translational research in rare skin disease. Support was provided by a conference grant from the National Institutes of Health (National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS)) as well as by AGI Dermatics, the American Academy of Dermatology, the American Skin Association, Amgen, the BCCNS Life Support Network, DebRA of America, FIRST, Genentech, the Pachyonychia Congenita Project, Sirna Therapeutics, and the Skin Cancer/Organ Transplant Program Project Grant (NIAMS).

The invited speakers, many of whom had no previous involvement with skin science, as well as session moderators, scribes, and other attendees, totaling 140 persons, broadly represented patients, patient support groups, physicians, scientists, academics, large pharmaceutical companies, small biotech companies, venture capitalists, the National Institutes of Health (NIH) as a major funding agency, and the United States Food and Drug Administration (FDA) as the government regulatory agency. There was strong representation of senior dermatologists from both the United States and the European Union, providing a broad perspective on the translational research process. The first one-and-a-half days of the meeting were designed to familiarize participants with the various aspects of the drug development process and to highlight several areas of promising new approaches to treatment of rare, monogenic skin disease. The final half day was spent in discussion intended to separate real from perceived obstacles and to prioritize potential pathways to reduce those obstacles.

THE FOLLOWING TOPICS WERE ADDRESSED IN DISCRETE SESSIONS:

Drug development pathways

Anthony Quinn (Roche, Palo Alto, CA) and Seth Stevens (Amgen, Thousand Oaks, CA) set the stage for ensuing discussion by outlining the usual steps in the drug development process and the kinds of obstacles that might be encountered at each stage. During the general discussion it became clear that there is a recent tendency for large pharmaceutical companies to enter drug development at increasingly later stages. Quinn emphasized that drug discovery and development is a complex process with many potential pitfalls; it requires a knowledge base that is distinct from that of academic medicine, and success often depends on effective multidisciplinary work. Stevens was the first of many to emphasize that interdisciplinary teams are critical to the development process.

Financial issues

Luke Evnin (MPM Capital, South San Francisco, CA), Geert Cauwenbergh (Barrier Therapeutics, Princeton, NJ), Lorne Taichman (State University of New York, Stony Brook/NY), and Howard Welgus (Pfizer, Ann Arbor, MI) represented, respectively, venture capital, a small pharmaceutical company, and two large pharmaceutical companies with established interests in skin. Evnin identified crucial factors that attract the various types of potential investors and the stage of development at which they might be willing to invest. Unmet

[1]*Department of Dermatology, University of California, San Francisco, California, USA;* [2] *Department of Dermatology, Boston University School of Medicine, Boston, Massachusetts, USA; and* [3]*Department of Dermatology, Yale University School of Medicine, New Haven, Connecticut, USA*

Correspondence: Dr. Leonard M. Milstone, Yale University School of Medicine, Department of Dermatology, 501 LLCI PO Box 208059, New Haven, Connecticut 06520-8059, USA. E-mail: leonard.milstone@yale.edu

needs, a plethora of which are found in rare skin disease, are a recurring focus of venture capital. Welgus reported that Pfizer was interested in bringing forth novel prescription pharmaceuticals for the treatment of common skin diseases and conditions. Big pharma's enthusiasm for therapies against rare, inherited disorders would be heightened if the targeted genes were found to have medical applicability to more common conditions. Cauwenbergh suggested that the regulatory scales had been tipped toward concern for risk as opposed to need for new drugs and noted that this imbalance was a serious disincentive for investors in drugs for rare diseases. Suggestions for righting the balance included extension of time for market exclusivity for such drugs; conditional trial approvals restricted to patients with the targeted disease with frequent review; and extension of the authority of the Orphan Drug Division of the FDA. Taichman advised the audience to think like an investor, not like a convert. He gave examples of how cell-based gene therapies faced particularly difficult regulatory hurdles because of the complexity of production issues. All emphasized that demonstrated efficacy in humans increasingly was expected by investors of all stripes.

Regulatory processes

Jonathan Wilkin (formerly FDA, Rocksville, MD) outlined the usual regulatory steps that apply to dermatologics. He urged developers to look beyond the "targeted" nature of the drug and seek empiric evidence for safety and effectiveness. Drugs intended for chronic use will receive additional scrutiny. Marlene Haffner (Office of Orphan Products Development, FDA, Rockville, MD) identified the special rules that apply to the development of orphan drugs. She indicated that her office exists to help the patient and the researcher. She gave examples of special programs her office uses to assist in the development of products to treat rare diseases. She noted that a common cause for delay in the regulatory approval process was poor understanding of the natural history or basic science of the disease, which leads to inappropriate endpoints. There was discussion of how small numbers of patients scattered over great distances add layers of complexity to logistics and to the institutional review board approval process.

Small molecules for rare diseases

Fred de Sauvage (Genentech, South San Francisco, CA) described drug development targeted to the hedgehog pathway, emphasizing how increased understanding of complex biology both limits and dictates developmental efforts. John Reed (Burnham Institute, La Jolla, CA) described the new NIH initiative (the Molecular Library Screening Center Network) designed to help investigators to get over the hurdles of rapid throughput assay development, to identify lead molecules, and to encourage collaboration between academic institutions. Irwin McLean (University of Dundee, UK) described early stages of screening of small-molecule libraries for transcriptional regulators of keratin 6a expression.

Protein therapeutics

Emil Kakkis (BioMarin, Novato, CA) described the stirring odyssey of the development of Cerezyme, a protein replacement therapy for Hurler's disease which affects about 3,000 patients worldwide. Mark Sliwkowski (Genentech, South San Francisco, CA) spoke about Herceptin, a protein therapeutic targeted to a much larger market (breast cancer patients) that nevertheless might have been abandoned if understanding of the biology of the disease had not kept pace with the development process. Both speakers described the technical, regulatory, and financial hurdles encountered in bringing systemically administered protein therapeutics to market. Dan Yarosh (AGI Dermatics, Freeport, NY) spoke about the difficulties of getting a topical protein therapeutic, T4 endonuclease V (T4N5), to market for xeroderma pigmentosum and the need for separate new investigational new drug applications (INDs) for individual disease indications. His comments made clear that FDA approval is sometimes elusive, despite apparent intentions to the contrary. David Woodley (University of Southern California, Los Angeles) spoke about preclinical success of injected collagen VII in animals with recessive dystrophic epidermolysis bullosa. He indicated that he would be ready to do human clinical trials, if he could make large amounts of the protein in a good manufacturing practice (GMP) facility. As happens so often, that last critical production step is beyond the resources of a university-based laboratory, and the small size of the target patient population discourages investors. Heiko Traupe (University of Münster, Germany) described early efforts to produce biologically active transglutaminase 1 for replacement in lamellar ichthyosis.

Targeting translation/transcription

Several methods for reduction of specific mRNA targets were presented. Joseph Carroll (Sirna Therapeutics, Boulder, CO) has used small interfering RNA (siRNA) to deplete the hr transcription factor, which in turn depletes mRNAs necessary for hair growth. His company has a phase I trial of siRNA ongoing in macular degeneration, and he discussed the medicinal chemistry and formulation needed to improve pharmacokinetics and to secure intellectual property rights. Frank Bennett (Isis Pharmaceuticals, Carlsbad, CA) reported that there has been tremendous progress in advancing antisense technology for the treatment of many systemic diseases. Local delivery, however, to cells in the skin by either systemic or topical routes remains an issue. He described an antisense RNA that led to substantial depletion of ICAM expression in epidermis in preclinical models but failed to have a significant effect when applied topically to patients with psoriasis. He indicated that failure to translate animal experience to human disease can be related to poor understanding of the role of the target in human disease or to differences in delivery parameters in animals compared with humans. He suggested that companies such as his are often willing to provide technology to funded investigators, who are interested in clinically well-understood targets and have potential investors standing by. He gave examples of ongoing collaborative trials targeting SOD1 inamyotrophiclateral sclerosis and apolipoprotein B in familial hyperlipidemia. Roger Kaspar

(TransDerm, Santa Cruz, CA) described siRNA suppression of mutant keratin, 6a *in vitro*, and long-lived suppression of reporter gene expression in mouse epidermis following intradermal injection. Moving those promising observations to trial in patients with pachyonychia congenita is his immediate challenge.

Targeting DNA

Peter Glazer (Yale University, New Haven, CT) talked about using triplex-forming oligonucleotides, and Michael Holmes (Sangamo, Boulder, CO) talked about using zinc-finger nucleases to recruit DNA repair enzymes in conjunction with simultaneously administered, homologous donor oligonucleotides to introduce site-specific sequence changes in DNA. Stable correction in cell lines and in mouse models has been achieved by both methods. Delivery issues are in large part responsible for low efficiency but can theoretically be overcome by repeated treatment or biological selection of the targeted cells. Paul Khavari (Stanford University, Stanford, CA) gave two examples of preclinical success using lentiviral vectors: replacement of transglutaminase 1 in cells from patients with lamellar ichthyosis and of collagen VII in fibroblasts from patients with recessive dystrophic epidermolysis bullosa. Unfortunately, scale-up issues and the regulatory climate following several viral vector-related adverse events in other clinical trials have impeded movement of that work into the clinic. One potential technical obstacle for certain types of *in vivo* gene therapy will be low-efficiency methods that target less than 100% of cells. When new genes are introduced into keratinocytes or fibroblasts, loss of gene expression has been a repeatedly observed problem. One reason for lost expression is that targeted cells have no selective advantage over normal cells. Jonathan Vogel (NIH, Bethesda, MD) showed that co-introduction of a selectable marker the multidrug resistance gene (MDR), with the target gene, followed by topical selection with colchicine, resulted in improved percentage and persistence of gene-targeted cells.

Miscellaneous issues

Sherri Bale (GeneDx, Gaithersburg, MD) spoke about how genetic heterogeneity in clinical diagnosis might affect the success and evaluation of therapeutic trials. Dennis Roop (Baylor College of Medicine, Houston, TX) described the value of engineered mouse models both for understanding of the pathophysiology of genetic skin disease and for preclinical testing. Discussion focused on the encouragement investigators take from success in animal models contrasted with the not infrequent failure of animal models to predict success in the clinic, and the current reluctance of venture capital and industry to join a translational effort until success in humans has been established. Soosan Ghazizideh (Columbia University, New York, NY) described how immune responses are likely to limit the effectiveness of cutaneous gene therapy and emphasized the need for studies directed at modulating destructive immune responses. Eugene Bauer (Neosil, Emeryville, CA, and formerly Stanford University, Stanford, CA) described how academic, industry, and regulatory cultures and policies (including those regarding conflicts of interest) impede the translation of basic discoveries to innovative patient therapies. He provided examples of how misunderstanding, mistrust, and disrespect between those cultures can impede translational research. Steve Katz (NIH, Bethesda, MD) outlined the new NIH road map and described new NIH initiatives designed to promote translational research. NIH acceptance of central institutional review boards for clinical trials could have a role in facilitating rare-disease trials. Margaret Kripke (MD Anderson Cancer Center, Houston, TX) described how and why the university research community discourages a teamwork approach to research. She noted that the President's Council on Cancer Research has suggested several areas in which a new system of rewards might begin to solve that problem: seed money, publication and grant review, and priority for collaborative research.

BREAKOUT DISCUSSIONS AND CONCLUDING SESSION

Conference speakers and attendees were assigned or self-assigned to one of four discussion groups after the last of the eight plenary sessions to distill the issues discussed, to consider what might be done, and finally to make recommendations for group action. The assigned topics were Obstacles to Drug Discovery (Paul Nghiem, moderator), Obstacles to Translation of Promising Therapies (Irene Leigh, moderator), Obstacles in Institutional Cultures (Kevin Cooper, moderator), and Obstacles to Gathering Funds (Klaus Wolff, moderator). These deliberations, also available on the conference web site (http://www.obstacles.medschool.ucsf.edu), were summarized for each group by its designated group leader. At the final joint session, the following conclusions received strong support:

Focus

We are overly rich in molecularly defined, rare skin diseases worthy of treatment. There are also many promising, unique, and complementary technologies poised for clinical development. As a concerned community, the participants recognized that successful treatment of a limited number of diseases would likely enable more rapid translation of treatments for many additional diseases. Therefore, concentrating resources on a small number of clinical targets to achieve proof of concept makes strategic sense.

Educate and communicate

Clear understanding of the biology of these rare diseases will be crucial for undertaking and completing therapeutic trials. Dermatologists will play a central role in that effort, but there are few existing models or mechanisms for learning the complexities of devising valid clinical metrics and ushering successful protocols through the drug development process or regulatory hurdles. Existing dermatological institutions should be called upon to establish programs for information exchange, access to learning resources, and identification of partners willing to help facilitate the complexities of bringing drugs for rare diseases to market.

Devise a novel institutional structure

There is a widening gap between discovery of promising drugs in model

systems and sufficient information to entice venture capital or industry to become involved in the development effort. No existing institutional structures are ideally suited to bridge this gap. Therefore, a new structure may be needed to push forward translation of products for rare skin disease.

Reward collaboration

Collaboration and cooperation, a central feature of the business culture, will be critically important if development of drugs is to become routine rather than exceptional. Existing institutions, including universities, journals, societies, and patient support groups, will need to move their cultures toward reward systems that encourage collaborative efforts. Broad institutional and regulatory acceptance of central institutional review boards would be one example. Recognizing collaborative rather than principal-investigator-style research accomplishments through promotion and other academic rewards would be another.

RECOMMENDATIONS AND NEXT STEPS

The very intense and fast-paced nature of the conference, held on the eve of the Annual Meeting of the American Academy of Dermatology, which many of the conference participants planned to attend, precluded thoughtful digestion of all the information presented. Participants have continued to interact with the conference organizers and each other, but at this writing, much remains to be done in order to meet the implicit goal of enhancing treatment options for genodermatoses. The major conclusion reached by the participants was that the conference had served a critical catalytic function in bringing together individuals of diverse backgrounds, strongly committed to translational research and specifically to developing therapies for genodermatoses, based on recent scientific advances. There was unanimous agreement that the exchange among the different groups — patients and patient advocates, clinicians, physician-scientists, basic scientists, industry scientists, representatives of the biotechnology and pharmaceutical industries, federal regulators, funding agencies, financiers, venture capitalists, and entrepreneurs — was exceedingly informative and led to invaluable networking at many levels. To capitalize on this important beginning, the organizers are planning a follow-up meeting in the form of a workshop during the March 2007 Annual Meeting of the American Academy of Dermatology in Washington, DC. Details of this meeting will be forthcoming.

**The Obstacles to Translation Conference was held at the University of California, San Francisco, California, USA, 1–2 March 2006.*